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Canadian Adverse Reaction Newsletter

Volume 15 • Issue 1 • January 2005

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_newsletter_e.html

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Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

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Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Telithromycin (Ketek) and warfarin: suspected interaction

Telithromycin (Ketek) is a novel antimicrobial that belongs to a new chemical family, the ketolides.[1] Ketolides are recent additions to the macrolide-lincosamide streptogramin class[1] and are designed to treat macrolide-resistant respiratory tract pathogens.[2,3] The Ketek product monograph states that, in a study involving healthy volunteers, there were no pharmacodynamic or pharmacokinetic effects on racemic warfarin.[1]

From May 29, 2003 (the date of marketing in Canada) to Sept. 15, 2004, Health Canada received 25 reports of suspected adverse reactions involving telithromycin. Seven reports were of coagulation disorders, 6 of which involved an interaction with warfarin and 1 an interaction with an unspecified oral anticoagulant. The patients' ages ranged from 50 to 79 years. The international normalized ratio (INR) was increased in 6 of the 7 reports and decreased in 1. Five patients had an INR that had previously been stabilized with warfarin; in the other 2 reports this information was not provided. Depending on when the patient's INR was due to be monitored, the change in INR was noted from 1 to 9 days after initiation of telithromycin. In 6 of the 7 cases, changes in one or both of the warfarin and telithromycin doses were required.

Telithromycin is metabolized by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 1A (CYP1A).[1] Warfarin exists as a racemic mixture of *R*- and *S*-warfarin. The *S*-isomer, metabolized by CYP2C9, is primarily responsible for the hypoprothrombinemic activity. The *R*-isomer, metabolized by CYP1A2 and to a lesser extent by CYP3A4, is less pharmacologically active than the *S*-isomer, but significant drug interactions have resulted from inhibition of its metabolism.[2,4]

Proposed mechanisms of interaction between telithromycin and warfarin include the presence of infection affecting the activity of cytochrome P450 and inhibition of the metabolism of the warfarin *R*-isomer.[2] Telithromycin is a substrate and inhibitor of CYP3A4. Its concentrations may be increased with concomitant administration of CYP3A4 inhibitors (e.g., ketoconazole), and telithromycin will increase the concentrations of other drugs metabolized by CYP3A4.[5] Antibiotics have been reported to decrease the intestinal flora that produce vitamin K, reduced concentrations of which impair prothrombin production. Also,

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genetics, age, diet (e.g., vegetables rich in vitamin K), fever, stress and concomitant medication could modify the metabolism of warfarin and affect the intensity of the resulting interaction.[6]

Although it has been stated that telithromycin does not interact with warfarin,[1,7] the prothrombin time and INR should be monitored closely,[2] especially in elderly patients, as should be the case whenever a new drug is started in a patient taking warfarin.

Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V); Iza Morawiecka, BScPhm, Health Canada

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Linezolid (Zyvoxam) and neuropathy

Linezolid (Zyvoxam), a synthetic antibacterial agent in a new class of antibiotics, the oxazolidinones, has been marketed in Canada since Apr. 6, 2001.[1] Linezolid is active against methicillin- and vancomycin-resistant gram-positive microorganisms.[2]

The safety and efficacy of linezolid given for longer than 28 days have not been evaluated in controlled clinical trials.[1] Dosage and administration guidelines recommend that treatment last no more than 28 consecutive days.[1] Because of its activity against resistant organisms that cause osteomyelitis and prosthetic joint infections, linezolid has been used in clinical practice for longer than the recommended treatment course.[2]

The long-term use of linezolid has been associated with severe peripheral and optic neuropathy.[2-4] In most cases the optic neuropathy resolved after stopping the drug, but the peripheral neuropathy did not.[4]

Health Canada has received a report of a 71-year-old woman who received linezolid, 600 mg twice daily, for an acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The patient received an initial 6-week course of linezolid, stopped treatment for 4–5 months and was given the drug again for 8 months. Linezolid was stopped when the patient was admitted to hospital with anemia, pure red cell aplasia and severe peripheral neuropathy. She had initially noticed numbness in her feet a month previously. At the time of the report, the anemia had resolved but the neuropathy had not. Novo-Hydrazide was also considered a suspect drug.

Neuropathy (peripheral or optic) has rarely been reported in patients treated with linezolid and has primarily occurred in patients treated for more than the maximum recommended duration of 28 days.[1] Myelosuppression including anemia is listed in the product monograph under warnings and postmarketing experience.[1] Pure red cell aplasia is not listed in the product monograph.[1]

Health care professionals must be aware of the potential for serious adverse reactions, including neuropathy, when linezolid is used beyond its recommended duration.[2] Spontaneous reporting of adverse reactions is an important aspect of postmarketing surveillance and contributes to maintaining the most up-to-date safety information on health products.

Debra Willcox, BSP, Health Canada

References

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Safe use of health products containing camphor and eucalyptus oils

Camphor and eucalyptus oils are contained in many over-the-counter health products, including topical rubs and products used for steam inhalation in the management of coughs and colds. Because these products are generally thought to be without health risks, they are often left accessible to young children, who may accidentally ingest them. Simple precautions, such as carefully reading the product label warnings and storing the products away from the reach of children, can help in preventing accidental poisonings. Further consultation with a health care provider is advised with regard to the appropriate use of these products. More information on this topic is available in the *It's Your Health* article at **www.hc-sc.gc.ca/english/iyh/index.html**.

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Adverse reaction reporting by health care professionals and consumers

Why report?

All marketed health products have benefits and risks. Although health products are carefully tested for safety and efficacy before they are licensed, some adverse reactions* may not become evident until the general population uses a health product under "real life" circumstances. By submitting a suspected adverse reaction report, you are contributing to the ongoing collection of safety and effectiveness information that occurs once health products are marketed.

Reported adverse reaction information may **contribute** to:

- the identification of previously unrecognized rare, or serious adverse reactions;
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Health Canada, through the Canadian Adverse Drug Reaction Monitoring Program, is responsible for collecting and assessing adverse reaction reports for the following health products marketed in Canada: pharmaceuticals, biologics (including fractionated blood products as well as therapeutic and diagnostic vaccines), natural health products and radiopharmaceuticals.

You do not have to be certain that a health product caused the reaction in order to report it. Adverse reaction reports are, for the most part, only *suspected* associations.

We want to know about all suspected adverse reactions, **but especially if they are:**

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c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
adr@dpic.ca

Saskatchewan
Saskatchewan Regional AR Centre
c/o Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
sask.ar@usask.ca

Ontario
Ontario Regional AR Centre
c/o LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
London ON N6A 5A5
adr@lhsc.on.ca

Québec
Québec Regional AR Centre
c/o Drug Information Centre
Hôpital du Sacré-Coeur de Montréal
5400, boul. Gouin ouest
Montréal (QC) H4J 1C5
pharmacovigilance.hsc@ssss.gouv.qc.ca

Atlantic
Atlantic Regional AR Centre
For New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador
c/o Queen Elizabeth II Health Sciences Centre
Drug Information Centre
2421–1796 Summer St.
Halifax NS B3H 3A7
adr@cdha.nshealth.ca

All other provinces and territories
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9
cadrmp@hc-sc.gc.ca

Reporting adverse incidents associated with medical devices
Health Products and Food Branch Inspectorate
Health Canada
AL 3002C
Ottawa ON K1A 0K9
Medical Devices Hotline: 800 267-9675

Visit Health Canada's Web site to obtain copies of the Medical Devices Problem Report Form (www.hc-sc.gc.ca/hpfb/inspectorate/md_pro_rep_form_tc_e.html) and guidelines on mandatory and voluntary problem reporting for medical devices (www.hc-sc.gc.ca/hpfb/inspectorate/man_vol_pro_rep_md_entire_e.html).

Caffeine-containing natural weight loss product and myopathy

A 47-year-old woman experienced muscle twitching over 4 months while taking the product Hydroxycut (Ephedra Free, by MuscleTech) for weight loss. The patient complained of muscle pain and weakness. Examination indicated fasciculations of the calf muscles and a creatine kinase (CK) level of 1021 (normally ≤ 190) U/L. Within 5 days of discontinuing the product, muscle symptoms resolved, and the CK values approached normal. Although no pre-existing medical conditions were noted, concomitant medications included Lomotil, Motilium, Nexium and Symbicort Turbuhaler.

Although Hydroxycut is not authorized for sale in Canada, it is used as a weight loss or bodybuilding product. The product was reformulated to be ephedra-free in January 2003. The new formulation, according to the product label, contains calcium, chromium, potassium, Hydroxagen Plus (which contains *Garcinia cambogia* extract, glucomannan, alpha lipoic acid, willow bark extract and L-carnitine) and Hydroxy Tea (which contains green tea leaf extract, caffeine and guarana extract standardized for 200 mg caffeine).

The association between caffeine intoxication and rhabdomyolysis has been documented.[1,2] Two cases of rhabdomyolysis associated with weight loss or bodybuilding products that contain *G. cambogia* or guarana or both, as in Hydroxycut, have been reported in the literature. One involved a product containing guarana, ephedrine, chitosan, *Gymnema sylvestre*, *G. cambogia* and chromium,[3] while an earlier case was associated with a product containing guarana, ginkgo and kava.[4] It is also possible that other ingredients contained in Hydroxycut (Ephedra Free), such as *G. cambogia* (which contains hydroxycitric acid) and chromium picolinate, may play a role in the development of rhabdomyolysis.[5]

Natural health products used for weight loss and bodybuilding may contain caffeine from a variety of natural sources, including guarana, green tea, kola nut and yerba maté. Consumers may unknowingly increase their intake of caffeine significantly and thereby increase their risk of caffeine-related adverse reactions, including rhabdomyolysis.

Jenna Griffiths, MSc, PhD, Karen Pilon, RN, Health Canada

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1. Wrenn KD, Oschner I. Rhabdomyolysis induced by a caffeine overdose. *Ann Emerg Med* 1989;18(1):94-7.
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Ceftriaxone (Rocephin) and immune hemolytic anemia in children

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Ceftriaxone antibodies appear to be induced by an immune complex mechanism during a sensitization phase after initial exposure to the drug.[2] Intravascular hemolysis may be triggered after subsequent re-exposure. The signs and symptoms of drug-induced IHA include severe hemolytic anemia, hemoglobinuria, hypotension, acute renal failure, fever and back pain.[3]

From Jan. 1, 1988, to Sept. 15, 2004, Health Canada received 1 report of acute hemolysis suspected of being associated with ceftriaxone. A young child with sickle cell disease had been given a single dose of ceftriaxone (80 mg/kg body weight) intravenously for fever and cough, and within 30 minutes developed a rash, pallor and decreased level of consciousness. Laboratory examination showed a positive direct Coomb's test result, a hemoglobin level of 7 g/L (the pre-infusion level was 110 g/L) and hemolyzed red blood cells. The following day, the patient died despite resuscitation attempts. The only concomitant medication was a single oral dose of erythromycin. The patient had been exposed to ceftriaxone in the past.

Nine pediatric cases of IHA associated with exposure to ceftriaxone were identified in the literature, 6 of which were fatal.[4-12] One child with sickle cell anemia received ceftriaxone on several occasions and experienced 6 episodes of unexplained transient hemoglobinuria before the onset of the IHA.[10]

Drug-induced IHA is associated with a high mortality rate.[3] Other than supportive care and red blood cell transfusion, there are few effective treatment options. Reintroduction of the drug is contraindicated because of the high risk of recurrence of hemolysis, which is often more severe.[3]

IHA associated with ceftriaxone is rare and has been reported to occur with repetitive, intermittent use of this drug. Children with underlying conditions such as hemoglobinopathies and immunodeficiencies are likely to require frequent treatment or prophylaxis with ceftriaxone, which may place them at increased risk of IHA. The development of signs and symptoms of IHA, including hemoglobinuria or unexplained

Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Olanzapine (Zyprexa): suspected association with pulmonary embolism

A 22-year-old man (weight 95 kg, height 1.78 m) was prescribed Zyprexa, 20 mg at bedtime. About 6 months after the start of treatment he was admitted to hospital with a massive bilateral pulmonary embolism, confirmed by chest CT. An electrocardiogram revealed a normal sinus rhythm. The patient did not have deep venous thrombosis (DVT), and results of venous Doppler ultrasonography of the legs performed 3 days after admission were normal. Celexa, 20 mg/d, was the only concomitant medication reported. The patient had a prior history of depression, had borderline autism and smoked half a pack of cigarettes a day. His father had a history of DVT. Results of tests for inherited DVT (e.g., tests for prothrombin gene mutation, Factor V mutation, protein C, protein S and activated protein C resistance) were negative. The patient was treated with Lovenox and then warfarin. Zyprexa was tapered off, and risperidone was gradually started. Similar cases have been described in the literature.[1,2]

References

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National and regional adverse reaction centres

British Columbia
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adr@dpic.ca

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Saskatchewan Regional AR Centre
c/o Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
sask.ar@usask.ca

Ontario
Ontario Regional AR Centre
c/o LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
London ON N6A 5A5
adr@lhsc.on.ca

Québec
Québec Regional AR Centre
c/o Drug Information Centre
Hôpital du Sacré-Coeur de Montréal
5400, boul. Gouin ouest
Montréal (QC) H4J 1C5
pharmacovigilance.hsc@ssss.gouv.qc.ca

Atlantic
Atlantic Regional AR Centre
For New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador
c/o Queen Elizabeth II Health Sciences Centre
Drug Information Centre
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Halifax NS B3H 3A7
adr@cdha.nshealth.ca

All other provinces and territories
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Marketed Health Products Directorate
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cadrmp@hc-sc.gc.ca

Reporting adverse incidents associated with medical devices
Health Products and Food Branch Inspectorate
Health Canada
AL 3002C
Ottawa ON K1A 0K9
Medical Devices Hotline: 800 267-9675

Visit Health Canada's Web site to obtain copies of the Medical Devices Problem Report Form (www.hc-sc.gc.ca/hpfb/inspectorate/md_pro_rep_form_tc_e.html) and guidelines on mandatory and voluntary problem reporting for medical devices (www.hc-sc.gc.ca/hpfb/inspectorate/man_vol_pro_rep_md_entire_e.html).

Caffeine-containing natural weight loss product and myopathy

A 47-year-old woman experienced muscle twitching over 4 months while taking the product Hydroxycut (Ephedra Free, by MuscleTech) for weight loss. The patient complained of muscle pain and weakness. Examination indicated fasciculations of the calf muscles and a creatine kinase (CK) level of 1021 (normally ≤ 190) U/L. Within 5 days of discontinuing the product, muscle symptoms resolved, and the CK values approached normal. Although no pre-existing medical conditions were noted, concomitant medications included Lomotil, Motilium, Nexium and Symbicort Turbuhaler.

Although Hydroxycut is not authorized for sale in Canada, it is used as a weight loss or bodybuilding product. The product was reformulated to be ephedra-free in January 2003. The new formulation, according to the product label, contains calcium, chromium, potassium, Hydroxagen Plus (which contains *Garcinia cambogia* extract, glucomannan, alpha lipoic acid, willow bark extract and L-carnitine) and Hydroxy Tea (which contains green tea leaf extract, caffeine and guarana extract standardized for 200 mg caffeine).

The association between caffeine intoxication and rhabdomyolysis has been documented.[1-4] Two cases of rhabdomyolysis associated with weight loss or bodybuilding products that contain *G. cambogia* or guarana or both, as in Hydroxycut, have been reported in the literature. One involved a product containing guarana, ephedrine, chitosan, *Gymnema sylvestre*, *G. cambogia* and chromium,[3] while an earlier case was associated with a product containing guarana, ginkgo and kava.[4] It is also possible that other ingredients contained in Hydroxycut (Ephedra Free), such as *G. cambogia* (which contains hydroxycitric acid) and chromium picolinate, may play a role in the development of rhabdomyolysis.[5]

Natural health products used for weight loss and bodybuilding may contain caffeine from a variety of natural sources, including guarana, green tea, kola nut and yerba maté. Consumers may unknowingly increase their intake of caffeine significantly and thereby increase their risk of caffeine-related adverse reactions, including rhabdomyolysis.

Jenna Griffiths, MSc, PhD, Karen Pilon, RN, Health Canada

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Nov 4 & Oct 29	Carbolith	Drug stability failure of a few lots of Carbolith 150 mg capsules — Valeant Canada Limited — consumer information and health professional communication
Oct 27	Oral-B toothbrushes and refills	Urgent product removal: Oral-B CrossAction Power and PowerMAX toothbrushes and refills — Gillette — consumer information
Oct 20	Ultrasound and medical gels	Risk of serious infection from ultrasound and medical gels — notice to hospitals
Oct 18 & 13	Eprex	Association of Eprex (epoetin alfa) with thrombotic vascular events — Janssen-Ortho Inc. — consumer information and health professional communication
Oct 14	Euro-K	Update on Euro-K recall lot EKT 404 and lot EKT 405 — letter to pharmacists
Oct 12	Permax	New safety information regarding Permax and occurrence of cardiac valvulopathy / fibrosis — Shire Biochem Inc. — consumer information and health professional communication
Oct 1	Vioxx	Merck Sharp & Dohme (MSD) announces voluntary worldwide withdrawal of Vioxx (rofecoxib) — Merck Frosst Canada Ltd — letter to pharmacists and health professional communication
Sept 30	Vioxx	Health Canada informs Canadians of Vioxx withdrawal by Merck & Co. — consumer information
Sept 29	Cochlear implants	Notification to Clarion 1.2 cochlear implant users; Notification to Clarion CII cochlear implant users; Notification to HiRes 90K cochlear implant users — Advanced Bionics — consumer information
Sept 27	Cochlear implants	Recall notification for all unused Advanced Bionics implantable cochlear stimulators — Advanced Bionics —health professional communication
Sept 7	LTV series ventilators	Safety information on the LTV series ventilators — Pulmonetic Systems — consumer information
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Acknowledgements
Expert Advisory Committee on Pharmacovigilance, Regional AR Centres and Health Canada staff

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ISSN 1499-9447, Cat no H42-4/1-15-1E

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